Ion Trap Mass Spectrometry: A Personal Perspective

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This paper is a personal perspective of the commercial development of the three-dimensional quadrupole ion trap mass spectrometer. Early ion trap invention and development which dates back to 1953, is described. The development of the ion trap is traced through three ages with the last age being where commercial development takes place. Key technical breakthroughs in ion trap technology and commercialization are presented and described up to the present time. (J Am Soc Mass Spectrom 2002, 13, 589–596) © 2002 American Society for Mass Spectrometry

All of us engaged in science face exciting opportunities every day. Our work often validates and strengthens the knowledge developed by gifted researchers who have preceded us. And, sometimes, we are fortunate enough to test new ideas and hypotheses that help move knowledge and understanding in new directions. The development of the commercial quadrupole ion trap mass spectrometer demonstrates these two basic trends in scientific research.

Those of us who worked at Thermo Finnigan developing the commercial ion trap mass spectrometer owe a great debt to those who preceded us, notably Wolfgang Paul, Hans Dehmelt and Norman Ramsey, who jointly won the Nobel Prize for Physics in 1989 (Figure 1). Much of our work validated and was built on the research of these men, especially Professors Paul and Dehmelt, who focused on development of the quadrupole ion trap for mass spectrometric applications.

The fundamental theory for all electrodynamic quadrupole field devices was developed by W. Paul and H. Steinwedel [1,2]. Their work predicted the force on an ion due to the quadrupole field in each of the three dimensions and led to the insight that all ions in the quadrupole field could be represented on a stability diagram. This stability diagram allows the researcher to predict whether a particular ion will have a stable trajectory (ion motion displacement is finite in time) or have an unstable trajectory (ion motion displacement becomes infinite in time). Specifically, Dr. Paul's work enabled scientists to know if an ion would be stable (trapped) or unstable (ejected) based on the position the ion has in the stability diagram. The stability diagram for a three dimensional quadrupole ion trap is shown in Figure 2. To determine the position an ion occupies on the stability diagram one simply maps the ion onto the a and q coordinates using the equations shown in the figure.

The central green region in the diagram represents an overlap of stability in both the radial (r) dimension and the axial (z) dimension in the ion trap. All ions that map inside this central region will have quadrupolar stability in both dimensions. By appropriate adjustment of parameters and operating conditions, ions can be made to have stability in only one dimension. And finally, ions can be made to map such that they are unstable in both radial and axial dimensions.

The ion trap itself consists of a ring electrode and two end cap electrodes. Theory says that to generate a quadrupole field in the ion trap the inner surfaces of all the electrodes are to have a hyperbolic profile and each electrode must be placed at a unique position.

Figure 3 shows the original ion trap assembly that was first fabricated in late 1979. The ion trap assembly is mounted on top of a stainless steel tube containing the electron multiplier ion detector. The quadrupole ion trap assembly itself consists of the ring electrode and two end cap electrodes which are held in the proper position by two identical alumina spacer rings. A ring electrode and an alumina spacer are shown together in an enlarged area of Figure 3. The alumina spacer rings provide the voltage isolation necessary to operate and scan the ion trap analyzer. Up to 6 kV of RF voltage can be applied between the ring and end cap electrodes to produce the trapping and scanning quadrupole field. The alumina spacers must be designed to withstand the high voltages that are present on the ion trap electrodes.

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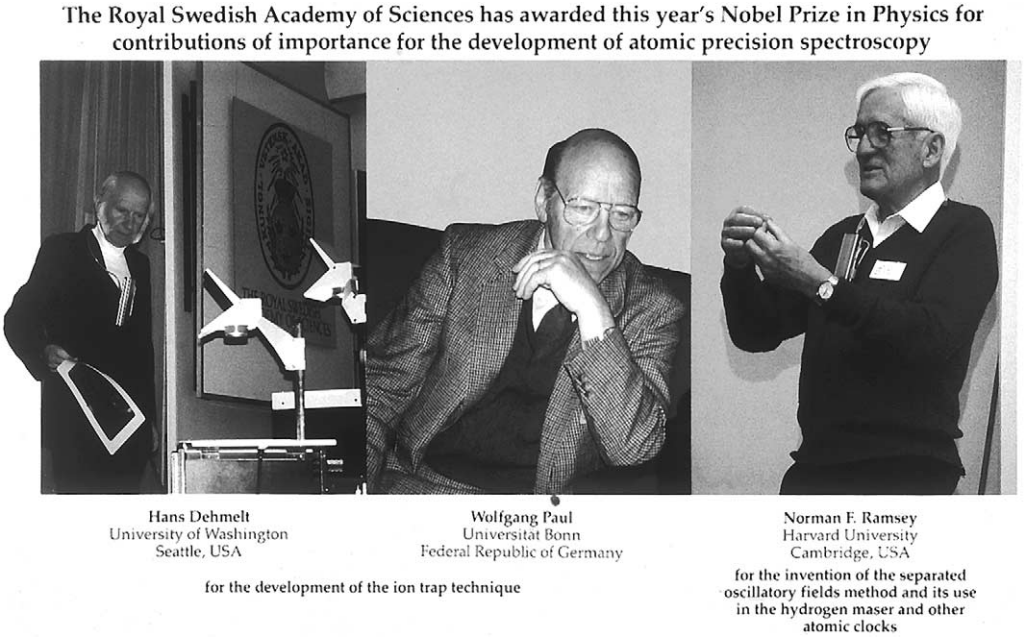

Figure 1. Poster displaying the 1989 Nobel Prize in Physics for the development of the quadrupole ion trap technique. Published by courtesy of the Royal Swedish Academy of Science.

Three Ages of Ion Trap Mass Spectrometry

The development of the quadrupole ion trap for use in mass spectrometry has been suggested by Raymond E. March and Richard J. Hughes in their book entitled *Quadrupole Storage Mass Spectrometry* [3] as being divided into three ages. Professor W. Paul and H. Steinwedel were the first to disclose a method for mass analysis by trapping a range of ion masses in the

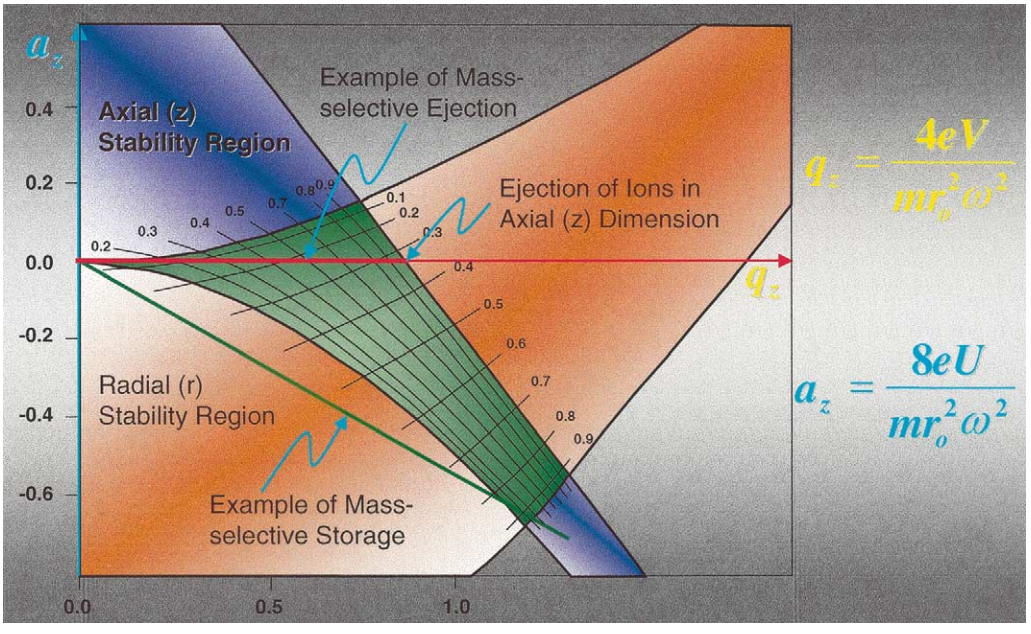

Figure 2. Portion nearest the origin of the quadrupole ion trap stability diagram using a and q parameters for the coordinate axes. V = zero-to-peak amplitude of the radio frequency (RF) voltage applied to the ring electrode; U = amplitude of direct current (DC) voltage applied to the ring electrode; r_0 = hyperbolic radius of the ring electrode; m = mass of the ion; e = electric charge on the ion; $\omega = 2\pi f$ (angular frequency of applied RF voltage); and f being the frequency in hertz. The blue region represents ion motion stability in the axial (z) dimension in the ion trap. The red region represents ion motion stability in the radial (r) dimension in the ion trap. Ions that map onto the a and q coordinates and fall into the green region have stability in both axial and radial trap dimensions.

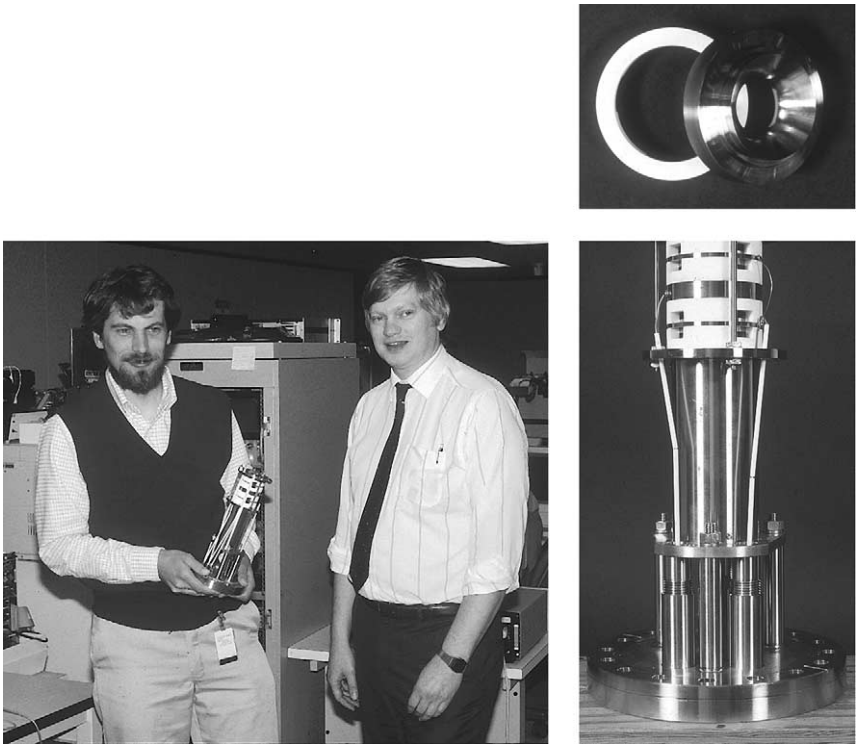

Figure 3. First research quadrupole ion trap analyzer designed and fabricated at Thermo Finnigan. The ring electrode is shown at the top with a corresponding alumina insulator. The radius (r_0) of the hyperbolic surface was approximately 1 cm for this ring electrode. The photographs were taken circa 1984; John E. P. Syka is to the left and I am to the right in the figure.

quadrupole ion trap and employing means to detect and measure the ions while stored. Their work can be seen in Figure 4 as the age of ion trap mass-selective detection.

The second age—mass-selective storage—took place during the late 1960s to the early 1980s. Scientists including P.H. Dawson, N.R. Whetten, John F. J. Todd and Raymond E. March were leaders in this age. This second scanning method involved producing a range of ion masses but operating the quadrupole storage field so as to store only a single mass in the ion trap at a time. This single ion mass is then ejected from the trap for detection by an external electron multiplier. The process is repeated rapidly until a complete mass spectrum is generated.

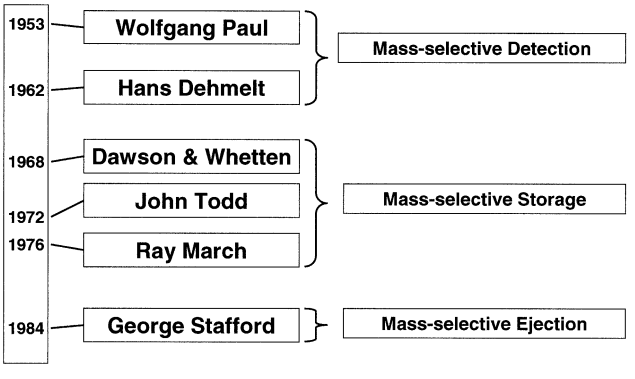

Figure 4. The three ages of Ion Trap Technology are shown as suggested by Raymond E. March and Richard J. Hughes.

The third age is called mass-selective ejection, and its development started in 1979 by me and included the work of other early researchers namely John E. P. Syka, Walter E. Reynolds, and Paul E. Kelley [4] (Figure 5).

Mass-Selective Ejection: An Answer to a Simple Question

Our insights at Thermo Finnigan came about by asking a simple question: What can be done to take full advantage of the unique properties of ion traps? The task was not to make an ion trap mass spectrometer work like other instruments; that would only have created a redundancy in the market. Instead, we wanted to use the ability of the ion trap in a new way so that researchers would gain new capabilities. Mass-selective ejection does this (Figure 6).

Using mass-selective ejection, an ion trap mass spectrometer takes a sample, ionizes it, and then traps ions over a large mass range of interest simultaneously. The trap can hold ions for surprisingly long periods of time, for example, we trapped some stable ions for 15 minutes or more. Once the ions are trapped, ions can be sequentially ejected in order of mass by adjusting the strength of the quadrupole field holding the ions. This is usually accomplished by ramping up the RF voltage applied to the ring electrode. The ejected ions are detected by an external electron multiplier to produce a mass spectrum.

Figure 5. Early ion trap researchers at Thermo Finnigan. (left to right: John E. P. Syka, George Stafford, Paul E. Kelley, and Walter E. Reynolds). This photograph was taken in our research laboratory in San Jose, CA, circa 1982. We are looking at an oscilloscope display of an ion trap mass spectrum (center of photograph). Also shown are the ion trap RF electronics, ion lens power supplies, and ion signal preamplifier to the right of the oscilloscope. Shown in the far right of the photograph is the in-house made computer system used for mass scan control and data acquisition. The ion trap vacuum manifold and associated pumping system, solid probe sample inlet, liquid sample inlet, and ion gauge with controller are behind the oscilloscope and are not visible in the photograph.

Early results from the mass-selective ejection scan technique are shown in the spectrum in Figure 7. This was an air/water background spectrum that was obtained by ionizing inside the ion trap (internal ionization) using an electron beam. The trapping RF voltage was operated at 2.281 MHz and the ring electrode hyperbolic radius (r_0) was approximately 1 cm. This mass spectrum was recorded by taking a Polaroid photograph of an oscilloscope trace displaying the ion signal output from the electron multiplier.

I think the idea of operating a quadrupole ion trap in the mass-selective ejection mode first came about by observing the operation of linear quadrupole mass filters with only RF voltages applied to the rod electrodes. These observations started around 1976, but I don't think I was the first to notice this behavior. Figure 8 is a diagram of an ion signal expected from a quadrupole mass filter operated with only an RF voltage applied.

This RF voltage is ramped from low to high amplitude. As this voltage is ramped, ions of increasingly

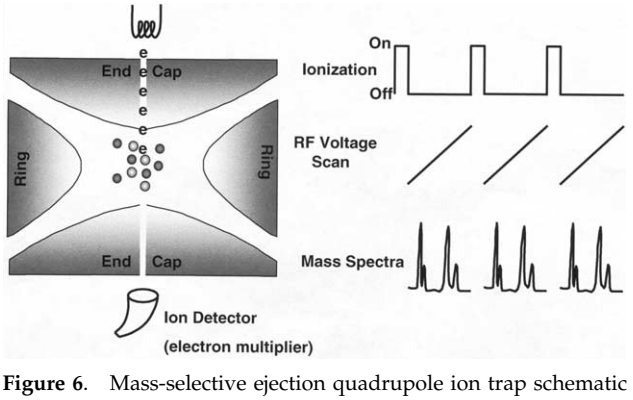

Figure 6. Mass-selective ejection quadrupole ion trap schematic showing internal ionization of sample molecules by electron ionization. The ionizing electron beam is turned on and off to control the timing of ion creation in the scan sequence.

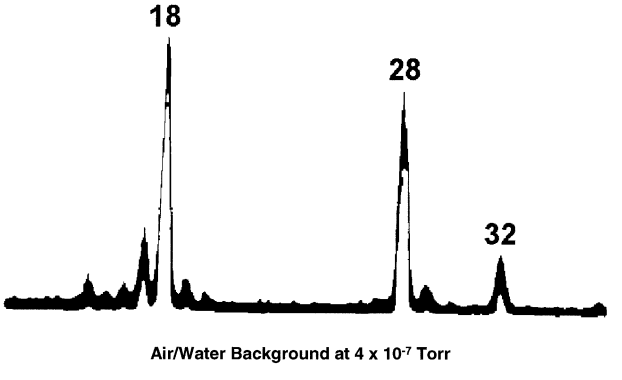

Figure 7. First mass-selective ejection spectrum acquired and recorded in spring 1980. The spectrum is from air/water background at 4×10^{-7} torr indicated ion gauge total pressure. An oscilloscope camera using Polaroid instant film was used to record the data.

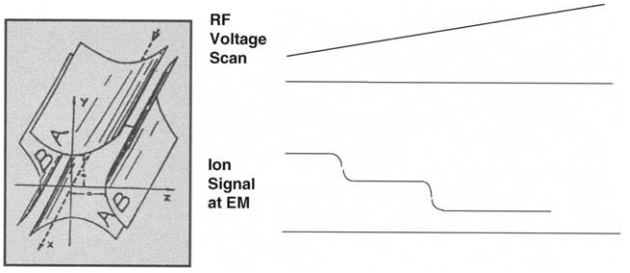

Figure 8. Quadrupole mass filter operated in RF voltage only scan mode showing total ion signal output to the electron multiplier ion detector (EM) when a continuous ion beam is injected into the mass filter.

higher mass become unstable in the quadrupole field and are not transmitted to the detector. In this case, the detected ion signal shows a total ion current that decreases at each event where a specific ion mass becomes unstable and is not transmitted to the detector. The first derivative of this detected ion signal would produce a mass spectrum, however, the signal to noise ratio is likely to be poor. This is because you are attempting to detect a small ion signal change in a relatively large transmitted total ion current. This is the case with the linear quadrupole mass filter operated in the continuous ion beam mode.

This problem with the signal to noise ratio is not present in an ion trap operated in the mass-selective ejection mode. Ions are formed or injected into the ion trap in a non-continuous or pulsed fashion. This means you do not have the large background ion current being continuously detected causing a noise interference.

Ion Trap Discoveries

In taking our concepts of ion trap mass spectrometry from idea to reality, several surprises confronted us. Some readily advanced our cause, while others presented challenges that had to be overcome.

The first surprise came in the area of pressurization. All the previous work on ion trapping mass spectrometry led us to believe that pressure background levels in the trap should be maintained less than 10^{-5} torr for best mass resolution and sensitivity. Due to commercial interest to evaluate the ion trap as a detector for a gas chromatograph, we began experiments with increasing the He pressure inside the ion trap vacuum manifold. I was concerned that raising the background pressure would only cause degradation of performance and was hoping that the results would not be too discouraging. On the insistence of Mike Story, Paul Kelley and I set out to add He gas to the manifold so as to raise the background pressure. To our amazement, the sensitivity and resolution appeared better especially at higher mass. We found an optimal pressure at around 1 mtorr, which was at the time an extraordinary discovery (Figure 9).

Our theory is that the He gas has the effect of collisionally damping the ion motion and causing the ions to migrate to the center of the ion trap, as shown in Figure 10. Since we believe the quadrupole field is more homogeneous in the center of the trap, ions stored closer to the center will experience a more uniform ejection process leading to improved mass spectral performance.

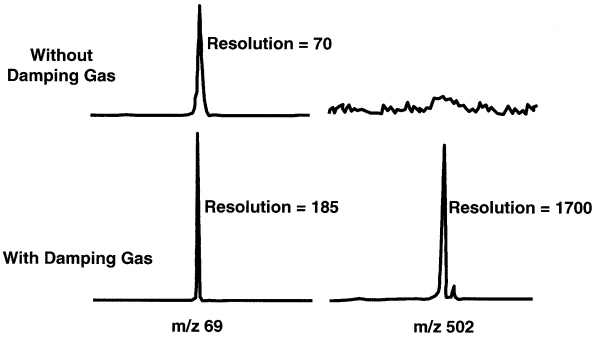

Figure 9. Effect of damping gas on peak shapes and resolution in the quadrupole ion trap operated in the mass-selective ejection mode. The data shown are for electron ionization generated fragment positive ions from perfluorotributylamine. Helium was used as the damping gas at approximately 1 mtorr actual pressure (calculated from ion gauge readings). The damping gas was added directly to the vacuum manifold and, therefore, the partial pressure of He in the quadrupole ion trap and in the manifold is approximately the same. Reprinted from *Int. J. Mass Spectrom. Ion Proc.* Stafford, G. C.; Kelley, P. E.; Syka, J. E. P.; Reynolds, W. E.; Todd, J. F. J. Recent improvements In and Analytical Applications of Advanced Ion Trap Technology, 1984, 60, 85-98, with permission from Elsevier Science.

The second surprise presented some difficulty. We found that while most results were correct, some mass peaks of known substances were being identified with a shift from the expected value [6]. Nitrobenzene, for example, was detected about *m/z* 0.5 lower than expected. We have referred to this type of mass shift, can be seen in Figure 11, in the ion trap as "chemical mass shift" since it depends on the chemical structure of the ion. This caused us some concern since we did not expect or understand this result.

We had a number of theories about why this was occurring, including concerns about the accuracy of the hyperbolic electrode surfaces, correctness of the ion trap

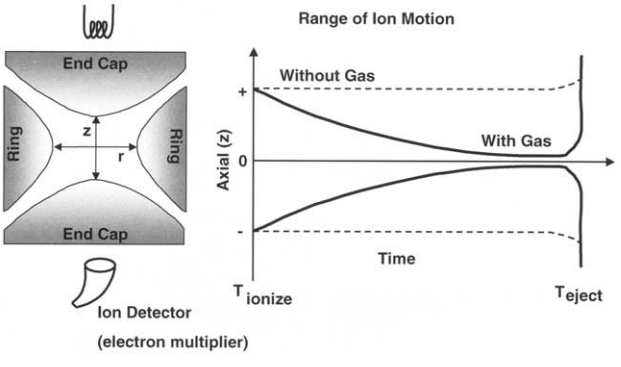

Figure 10. Theoretical damping of ion momentum in the quadrupole ion trap is schematically shown as a function of time from initial ion storage (T_{ionize}) to ion ejection (T_{eject}). The axial (z) and radial (r) axes are labeled in the ion trap diagram for reference.

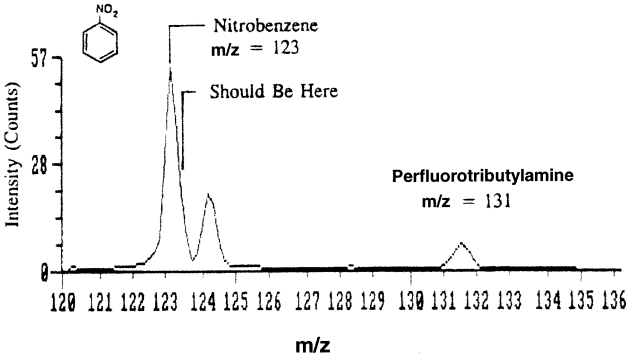

Figure 11. Chemical mass shift for nitrobenzene in the quadrupole ion trap operated in the mass-selective ejection mode. The ion trap assembly had theoretically correct hyperbolic electrode geometry. Reprinted with permission from *Practical Aspects of Ion Trap Mass Spectrometry, Vol. 1*, edited by Raymond E. March and John F. J. Todd. Copyright CRC Press, Boca Raton, Florida.

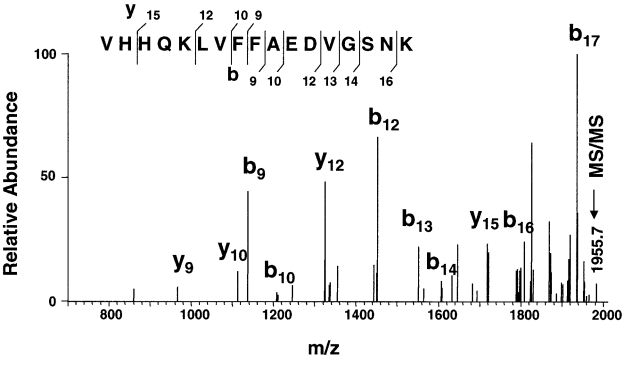

Figure 13. MALDI MS/MS spectrum of peptide precursor ion *m/z* 1955 recorded on a modified LCQ. Data were acquired with 1 fmol and a total scan time of 2 s. Printed with permission from B. Chait, Rockefeller University.

assembly, and perturbation of the quadrupole field due to end cap apertures. Upon extensive examination of the ion trap mechanical design and the tolerances of the actual device, we found no errors that we believed to be causing the problem.

Fortunately, we did find a solution to our problem without too much difficulty. We found by experimentation that stretching each end cap away from the ring electrode by 0.030 of an inch did minimize the mass shift to give us good mass assignments (Figure 12). My current theory to why this works is that the stretch helps to correct a quadrupole field perturbation caused by the apertures in the end caps. The end cap apertures add a negative octopole field component to the main quadrupole field. Stretching the end caps add a positive octopole field component, thus, tending to correct for the aperture perturbation.

A third surprise was once again extremely encouraging and analytically important. Our belief was that ion trap mass spectrometry would work well as an instrument for MS/MS analysis of small molecules. We doubted, however, that it would be a useful tool for studying large molecules such as peptides. The reason was that our preferred tool for fragmenting ions was CAD using He gas at approximately 1 mtorr. Since He has an atomic weight of 4 u, it would seem that the efficiency for fragmentation of an ion with a *m/z* 400 or greater would be too low to be analytically useful. However, results from MS/MS on peptide precursor ions have shown very efficient fragmentation yielding product ion spectra that are easily searched against computer libraries for identification.

B. Chait and A. Krutchinsky at Rockefeller University [5] have modified an LCQ™ ion trap mass spectrometer by equipping it with a MALDI source. The data produced by them in Figure 13 show that excellent product ion spectra are generated from the peptide precursor ion at *m/z* 1955 down to the 1 fmol level.

I think we underestimated the ability of the He collision gas at 1 mtorr to be persistent and undergo hundreds to thousands of collisions with the precursor ion to eventually add sufficient energy to cause fragmentation.

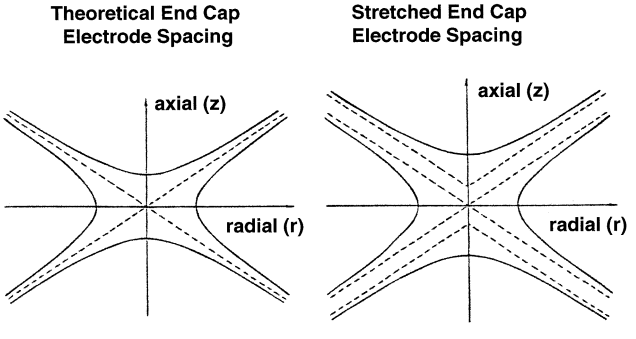

Figure 12. Cross sectional views for the quadrupole ion trap for theoretical and stretched end cap spacings. Reprinted with permission from *Practical Aspects of Ion Trap Mass Spectrometry, Vol. 1*, edited by Raymond E. March and John F. J. Todd. Copyright CRC Press, Boca Raton, Florida.

The Future

I believe future advancements in ion trap technology are likely to occur in the following areas:

- **Improved Accurate Mass Measurement**
- **Increased Ion Storage Capacity**
- **More Data Dependent Computer Control and Software Application Data Analysis**

Mass assignment accuracies are currently sufficient to identify peaks to within *m/z* 1 for a typical mass range of approximately *m/z* 5,000. With advancements in instrument mass calibration stability arising primarily out of minimizing electronic drifts, and continued understanding and control of the mass shift phenomena, mass assignment accuracies are going to continue to improve. For ions that show relatively small chemical mass shifts, Table 1 summarizes mass accuracies obtained on a modified LCQ system.

Note that in the Table, the modifications to a standard

Table 1. Results from accurate mass determination on a modified LCQ ion trap mass spectrometer

Instrument Modifications:	End-Cap Aperatures (in.)	End-Cap Spacers (in.)	Heated Capillary I.D. (μm)	Background Gas Pressure (torr)	Total Pressure with He (torr)
	0.030	0.010	300	3.9×10^{-6}	4.4×10^{-6}
	Compound Name			Theoretical Ion *m/z*	Charge State
Test Compounds:	(Arg^8) Vasopressin			542.7267	2
	Leucine Enkephalin			556.27707	1
	Bradykinin Fragment 1–5			573.31484	1
	Substance P			674.37183	2
	Oxytocin			1007.44417	1
	(Arg^8) Vasopressin			1084.44557	1
	Leutinizing Hormone Releasing Hormone			1182.58072	1
	Substance P			1347.73584	1
Average Results:	Mass Accuracy (mmu)		Precision (mmu)	Mass Accuracy (ppm)	Precision (ppm)
	5.901		2.832	9.660	3.473

LCQ include a reduced total internal ion trap operating pressure to 4.4×10^{-6} torr and a reduced end cap stretch to 0.010 inches per end cap. The mass accuracy and precision results, shown at the bottom of the table, are average values from the measured mass assignment data of the eight listed compounds. The same average results are listed in both millimass units (mmu) and part per million (ppm) units. The data were obtained by Jae Schwartz at Thermo Finnigan, San Jose, CA.

A very important second advance will come from increasing the ion storage capacity [7,8]. Examples of ion trap devices that have increased ion storage capacity are shown in Figure 14. The device to the left is similar to a conventional quadrupole mass filter, but has additional end sections to contain ions and a slot in the center of one or more rods to allow radial mass-selective ejection of ions for detection.

The device to the right also has a two-dimensional quadrupole field, but in this example the trap has a circular design allowing containment of ions without the use of end sections. I am confident that larger ion storage capacity will increase sample sensitivity and improve precision for mass assignment and ion abundance measurements.

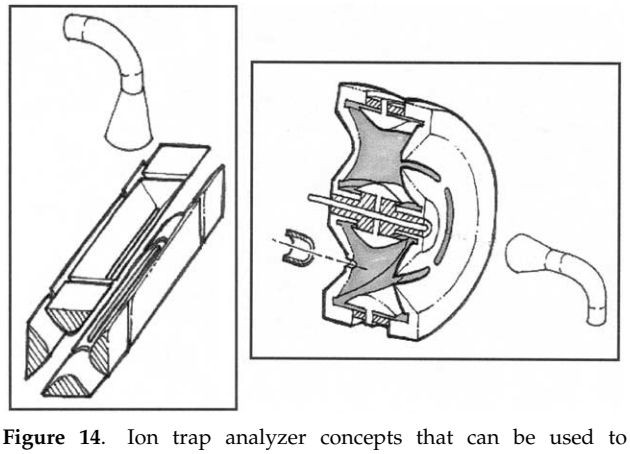

Figure 14. Ion trap analyzer concepts that can be used to significantly increase ion storage capacity. Electron multiplier ion detectors are shown to illustrate how ions might be mass-selectively ejected from the traps and detected.

Data dependent instrument control programs and software applications are crucial to the usefulness of ion traps. Perhaps no other mass spectrometer performance has been impacted by software as much as the quadrupole ion trap. Since all of the scan functions for single and tandem mass analysis are a complicated sequence of timed events, computer control of the scan is both vital and an opportunity to provide unique instrument performance. The data dependent scan function for tandem mass analysis is an excellent example of what can be done to automate and efficiently acquire data to solve a complex problem such as peptide identification. Without data dependent scan control and application software to help analyze the data, problems such as peptide identification would be far too slow to be of any real utility. I believe that new application software and data dependent instrument control will be the key driving force in pushing ion trap mass spectrometry into the most challenging areas of research.

Conclusion

Like most scientific development, the history of ion trap mass spectrometry demonstrates how researchers can collaborate and build on each other's work across international boundaries and across time. It also shows how productive research can proceed both by staying on the tried and true path and also by wandering off the path from time to time. I count it as a privilege to have been a part of this exciting development in ion trap

technology and to have worked with and known such good colleagues and friends.

Acknowledgments

The author would like to give special acknowledgment to John F. J. Todd and Raymond E. March for their dedicated efforts in pioneering and continued development of quadrupole ion trap technology. Colleagues at Thermo Finnigan also deserving special recognition are Dennis Taylor, Mike Story, and Jae Schwartz for their lifelong career efforts in ion traps. GS has always been impressed with John Syka's ability to understand ion trap phenomena from a fundamental theoretical basis and then apply this understanding to help develop practical approaches to ion trap advancements. The author also wants to acknowledge Don Hunt, his PhD research advisor, for his never-failing encouragement and friendship. And, finally, he wants to thank his parents and wife for their unconditional love and support.

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